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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/682,104	10/09/2003	Dorotea Raventos Segura	10298.200-US	9207
25908 7590 05/21/2007 NOVOZYMES NORTH AMERICA, INC. 500 FIFTH AVENUE SUITE 1600 NEW YORK, NY 10110			EXAMINER BAUGHMAN, MOLLY E	
			ART UNIT 1637	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/682,104

Applicant(s)

SEGURA ET AL.

Examiner

Molly E. Baughman

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. Applicant's amendments, and arguments, filed 3/6/2007, are acknowledged.
2. Applicant's arguments, see pages 6-7, filed 3/6/2007, with respect to claim rejections under 35 USC § 112 – second paragraph, 35 USC § 102 (Stiles et al. and Bylina et al.) and 35 USC § 103 (Stiles et al. and Shafikhani et al.) have been fully considered and are persuasive in view of amendments. The rejections of the corresponding claims have been withdrawn. However, new grounds of rejection have been made under 35 USC § 102 in view of Zauderer et al. (US 7,067,251), and USC § 103 in view of Bylina et al., and Shafikhani et al., necessitated by the amendments.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-10, and 12-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Zauderer et al. (US 7,067,251).

Regarding claims 1-10, and 12, Zauderer et al. teach a method where a library of insert polynucleotides are introduced into a population of host cells, and the expression of the target polynucleotide directly or indirectly promotes host cell death, wherein the

insert polynucleotides are collected from the host cells which undergo cell death (col.12, lines 26-34; col.15, lines 23-33). The method involves constructing a library of polynucleotides in a vector and transfecting host cells with the vector for induced expression (entire document, particularly, pg.14, lines 51-52). In various embodiments, Zauderer discuss method where gene products, such as proteins or peptides expressed in host cells function on that host cell after being secreted or may function on a second cell after being secreted (col. 19-20; col.42-43; col.109). The second cell may be the same type of cell as the host cell or may be a different type of cell from the host cell (col.109, lines 50-57). In Example 24, a first plurality of cells are introduced with a library of polynucleotides and are screened for an altered phenotype (col.145, lines 55-60). An altered phenotype includes cell viability, cell death – col.146, lines 30-33, 54-63 and col.42, lines 10-65). Additionally, in some embodiments, the library is introduced into a first plurality of cells, and the effect of the insert polynucleotides is screened in a second or third plurality of cells, different from the first, generally a different cell type (col.145, lines 60-65). This method can be done where the media from the first cells are allowed to touch the second plurality of cells or there may be direct contact between the cells (col.146, lines 1-6). The method also entails treating the cells to conditions suitable for the expression of the insert polynucleotide (i.e. inducible promoters) (col.146, lines 8-10). The cells are screened for exhibiting the altered phenotype, as described above (col.146).

Regarding claim 13, in some embodiments, the host cells which have undergone lysis, thereby release their cytoplasmic contents into the liquid medium in which said host cells are cultured (col.13, lines 33-36).

Regarding claims 14-19, specific embodiments of the invention fines use with infectious organisms and pathogens, where libraries are introduced into specific cell types where specific changes to cellular damage or apoptosis by the antibiotics are produced (col.53, lines 25-45; col.155, lines 45-55). These pathogens include various gram-positive and gram-negative bacteria, including *E.Coli*, as well as yeast and fungal pathogenic cells (col.53, lines 33-44).

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bylina et al (US 2002/0025537, cited in the previous Office Action).

Bylina et al. discuss a method of screening for an antimicrobial peptide by screening a library consisting of a collection or population of members (i.e. DNA molecules) (page 3) (claims 3 and 10). A DNA library can be screened by cloning the DNA fragments into an expression vector, transforming a suitable host cell, inducing expression of the gene product encoded by the DNA fragment, and initiating a reaction which indicates the presence of the desired activity (page 4) (claims 1, 3 and 5). In one embodiment, *E.coli* cells are used for an inducible expression system that expresses active antimicrobial peptides (page 5) (claims 1,3, and 16-18). It is also noted that transformation can occur with various types of cells (bacterial, yeast, algal, plant or animal cell (page 4). Cells used are intended encompass archaea, bacteria, and eucarya (page 5) (claims 14-20). Bylina discusses assays wherein the host cell is killed by the expression of the antimicrobial polypeptide via the cloned gene induced by IPTG and a live/dead viability staining is done to identify positive clones (pg.7, [0056-0057]).

Bylina also discusses methods where the host cells can also be used to express the peptide library only for the purpose of producing the peptides (i.e. host cell). Cells can be deposited onto a filter and then onto a nutrient medium for the colonies to grow (claim 1, part (b), claim 2 part (a)). They are then transferred to another medium

containing the inducer to initiate expression of a cloned gene (claim 1 part (c), claim 2 part (a)). If necessary, the colonies can be lysed by exposing them to chloroform vapor (page 6) (claims 12-13). The target cells, which indicate the effect of the peptides on cell viability, are grown on a second membrane filter and are placed in contact with the large library of peptide-expressing microcolonies to indicate which cells are producing an active peptide (page 9 and 11) (claims 1, 3, 5, 8, 10, and 12). Bylina states that the target cells may comprise E.Coli or another pathogenic organism (i.e. E.Coli is the host cell) (pg.9, [0077]). Positive clones are characterized by DNA sequencing (page 10 and 11) (claim 9). Bylina et al. antimicrobial peptides of the invention to be "divided into four major structural classes: (1) beta-sheet structures with multiple disulfide bonds, such as the defensins; (2) alphahelical structures, such as the cecropins and magainins; (3) extended coils with a predominance of one or more amino acids, such as indolicidin, and (4) loop structures with a single disulfide bond, such as lactoferricin" (page 3).

Although Bylina et al. discuss methods where the host cells are killed by the presence, synthesis, and/or expression of the antimicrobial polypeptide encoded by the polynucleotide sequence, as well as embodiments where the antimicrobial polypeptide expressed by the host cell are also used in assays where an indicator cell(s) is present and are sensitive to the expressed polypeptide, they do not specifically discuss a method where both embodiments are combined in one method.

One of ordinary skill in the art would have been motivated to modify the method of Bylina et al. where the host cells expressing the polypeptides in the presence of indicator cells are killed by the presence, expression and/or synthesis of the

polypeptides because Bylina discusses the benefits of using host cells which are killed by the expressed polypeptide during assays of screening antimicrobial polypeptides and also suggests that it may be necessary to kill the host cells in order to isolate the expressed gene (pg.6, [0056]). Therefore, the skilled artisan would have had a reasonable expectation of success in using one or more host cells which are killed by the presence, expression and/or synthesis of the antimicrobial polypeptides in the method of Bylina et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed host cells which are killed by presence, expression and/or synthesis of the antimicrobial polypeptides therein.

4. Claims 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bylina et al (US 2002/0025537, cited in the previous Office Action), as applied to claims 1-18 above, in view of Shafikhani et al. (1997, cited in the previous Office Action).

The teachings of the primary reference are stated above. While Bylina et al. describe using various bacteria as hosts and the importance of developing antibiotics against gram-positive bacteria (pg.1, [0004]), they do not specifically discuss the use of gram-positive bacterial cells or specifically, *Bacillus subtilis*, during their methods.

Shafikhani et al. discuss the use of *Bacillus subtilis* as a host in generating large libraries of mutants of the protease gene, which is actively secreted from the cell (page 305).

One of ordinary skill in the art would have been motivated to modify the method of Bylina et al. to use a gram-positive bacteria, specifically, *Bacillus subtilis*, as a host cell because the benefits of using *Bacillus subtilis* as a host cell for the generation of a library of peptides were shown by Shafikhani et al. The skilled artisan would have had a reasonable expectation of success in using *Bacillus subtilis* as a host cell in the method of Bylina et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed *Bacillus subtilis* therein.

5. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zauderer et al. (US 7,067,251), as applied to claims 1-10, and 12-19 above, in view of Bylina et al (US 2002/0025537, cited in the previous Office Action).

The teachings of Zauderer et al. are discussed above. Zauderer does not discuss the method wherein the antimicrobial polypeptide comprises disulfide bonds.

The teachings of Bylina are discussed above, specifically disclosing antimicrobial peptides comprising disulfide bonds.

One of ordinary skill in the art would have been motivated to modify the method of Zauderer et al. to screen polynucleotide sequences encoding an antimicrobial polypeptide comprising disulfide bonds because Bylina states that peptides containing such structures are shown to enhance the activity of conventional antibiotics and may serve as anti-resistance compounds and demonstrates the benefits of screening for such polypeptides (pg. 3, [0028]). The skilled artisan would have had a reasonable

expectation of success in screening for expressed antimicrobial polypeptides comprising disulfide bonds in the method of Zauderer et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed antimicrobial polypeptides comprising disulfide bonds therein.

6. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zauderer et al. (US 7,067,251), as applied to claims 1-10, and 12-19 above, in view of Shafikhani et al. (1997, cited in the previous Office Action).

The teachings of the primary reference are stated above. While Zauderer et al. describe using various bacteria being gram-positive bacteria, they do not specifically discuss the *Bacillus subtilis* during their methods.

Shafikhani et al. discuss the use of *Bacillus subtilis* as a host in generating large libraries of mutants of the protease gene, which is actively secreted from the cell (page 305).

One of ordinary skill in the art would have been motivated to modify the method of Zauderer et al. to use a *Bacillus subtilis* as a host cell because the benefits of using *Bacillus subtilis* as a host cell for the generation of a library of peptides were shown by Shafikhani et al. The skilled artisan would have had a reasonable expectation of success in using *Bacillus subtilis* as a host cell in the method of Zauderer et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed *Bacillus subtilis* therein.

Summary

7. No Claims are free of the prior art.
8. Any remaining rejections and/or objections not addressed above are withdrawn in view of the amendments and/or arguments.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Molly E Baughman
Examiner
Art Unit 1637

MEB 5/15/07

Kenneth R. Horlick
KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

5/16/07